REMARKS

Applicant thanks the Office for the attention accorded the present Application in the December 18, 2002, Office Action. In that Action, Claims 1-7, 9-11 and 13-17 were rejected under 35 USC §103(a) as being unpatentable over the Merck Manual Section 16, Chapter 202, Coronary Artery Disease.

Applicants respectfully traverse.

As previously explained, the present invention is based upon recognizing the serious consequences stemming from a failure of patients to avail themselves of, to receive and to take medication (in other words, patient compliance), particularly beta-blockers and platelet inhibitors. The present application teaches that despite compelling clinical evidence, many individuals at risk fail to benefit from such treatment. (Applicants' Disclosure: Page 2, lines 8-9). Large studies indicate that tens of thousands of lives could be saved each year if more people were utilizing a beta-blocker after having a heart attack. (Applicants' Disclosure: Page 2, line 26 to Page 3, line 2). The failure of patients to avail themselves of such treatment underscores the present need for the formulations of the present invention. (Applicants' Disclosure: Page 4, lines 16-18).

The Office states that the Merck Manual (page 14 submitted with the Office Action) recites that aspirin reduces mortality and reinfarction rates post-myocardial (MI) patients 15% to 30%. Timolol, propranolol or metoprolol reduces post-MI mortality by about 25% for >= 7 years. High-risk patients should be treated. The Office admits that

the Merck Manual does not teach these compositions together in a single dosage unit. In fact, the information provided by the Merck Manual is the same or similar information contained in Applicants' specification. The Merck Manual provides no new evidence (teaching, motivation or suggestion) to render Applicants' invention obvious. Unlike Applicants' invention, the Merck Manual contains no recognition of recurrent heart attacks or deaths that occur because individuals fail to receive treatment. Moreover, the Merck Manual contains no teaching or suggestion to remedy this problem. Applicants' invention seeks to prevent recurrent heart attacks and deaths, significant problems that continue to occur despite the information that is known and disclosed in the Merck Manual.

The Office relies on In re Kerkhoven, 205 USPQ 1069, for the proposition that it is prima facie obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.

The Office's reliance is misplaced and Kerkhoven is inapposite. Kerkhoven is a process claim case and cites to In re Crockett, 279 F.2d 274 (CCPA 1960), which contains the reference that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful **for the same purpose**, in order to form a third composition which is to be used for the **very same purpose**. The ruling is based on the use of two compositions each of which promotes the formation of a nodular structure in cast iron. The ruling in Kerkhoven is inappropriate in the present

application because the two compositions of the present application are not used for the **very same purpose** on two levels. On one level, the purpose of beta-blockers is to block nerve impulses to special sites (beta receptors) and to reduce the rate of heartbeats and the force of heart contractions. The purpose of platelet inhibitors is to inhibit the action of the blood clotting element (platelets) in the blood. In other words, beta-blockers cannot be used for inhibiting platelet action in the blood. Where the purpose of beta-blockers and platelet inhibitors are **not the same**, Kerkhoven is inapposite. On a second level, the purpose of combining a beta-blocker and a platelet inhibitor such as aspirin into a single dosage unit is to enhance patient compliance to a treatment regimen and to improve the utilization of both beta-blockers and platelet inhibitors.

Applicants disclose that beta-blockers and platelet inhibitors exist in the prior art. Applicants do not presume to claim that these medications are new. Applicants' invention contemplates an interventional measure that is neither within the scope of lay individuals nor presently available to lay individuals. As discussed in Applicants' disclosure, there is a need for cardiovascular preventive treatment and a need to overcome a failure of patients to avail themselves of such treatment. This underscores the need for the formulations of the present invention. Combining these agents to provide a single dosage unit for a user would simplify treatment, increase convenience, reduce cost, and enhance compliance with the use of medications that require long-term use.

The Office provides no evidence of teaching, motivation or suggestion in the prior art to support the Office's obviousness rejection. The Office simply relies on case law taken out of context to provide the suggestion.

Applicants' invention was conceived to provide the claimed cardiovascular medicaments in a single dosage unit for a user to help alleviate existing and on-going, long-term problems. Specifically, Applicants' invention is an attempt to simplify treatment, increase convenience, reduce cost, and enhance patient compliance, particularly in older patients where cardiovascular treatment regimens require taking multiple medications over long-term treatment periods.

Applicants provide further objective evidence in support of Applicants' claim of nonobviousness by way of the Declaration of Dr. Jerry H. Gurwitz. Dr. Gurwitz is a Professor of Medicine at the University of Massachusetts Medical School, Executive Director of the Meyers Primary Care Institute and one of the foremost authorities in the country for the treatment of the elderly and on the subjects of adverse drug events, drug prescribing and utilization patterns, and clinical decision-making in the elderly patient. Dr. Gurwitz may be considered one of extraordinary skill in the art, yet even Dr. Gurwitz believes that Applicants' invention is nonobvious and will provide a means to overcome problems in patient compliance and to improve upon present under-utilization of cardiovascular treatments.

Dr. Gurwitz has no financial interest in Applicants' invention and will not financially benefit directly or indirectly from the patentability of the present invention. In

fact, such a dosage unit for cardioprotection would likely reduce the number of cases of recurring myocardial infarction that he treats each year.

Dr. Gurwitz's declaration is relied upon as evidence of the knowledge possessed by not only one of ordinary skill in the art but also by the knowledge possessed by one having a higher level of knowledge than one of ordinary skill in the art (specialist in treating the elderly where noncompliance especially with multiple medications is a problem). As a disinterested party, Dr. Gurwitz's opinion evidence must be given serious weight, especially in view of the fact that the Office is only relying on misinterpreted case law as the basis to provide the motivation, suggestion or teaching to reject Applicants' claims for obviousness.

Yet, even Dr. Gurwitz's declaration confirms that one of extra-ordinary skill in the art is not one who undertakes to innovate. He knows first hand the problems with patient noncompliance in multiple medication treatment regimens, especially in the elderly. He is also aware of the need in the field to overcome these problems.

Secondary considerations must be given due weight by the examiner and the Board of Appeals during ex parte prosecution. *In re Sernaker*, 702 F.2d 989, 217 USPQ 1 (Fed. Cir. 1983). Objective evidence, composed of real-world facts, is entitled to **great weight** in a case. *Rosemount, Inc. v. Beckman Instruments, Inc.*, 727 F.2d 1540, 221 USPQ 1 (Fed. Cir. 1984) (emphasis added). Although objective factual evidence of obviousness or nonobviousness is preferable to opinion testimony, such testimony is entitled to some weight. Opinion testimony by a party with a direct interest

in the litigation is less persuasive than that of a disinterested party, but it may still be relied upon. *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985), *cert. denied*, 475 U.S. 1017 (1986). The secondary considerations are . . . essential components of the obviousness determination. *In re Rouffet*, 149 F.3d 1350, 47 USPQ2d 1453 (Fed. Cir. 1998). The consideration of the objective evidence presented by the patentee is a necessary part of the obviousness determination . . . The objective evidence of non-obviousness may be used to rebut a prima facie case of obviousness based on prior art references. *WMS Gaming, Inc. v. International Game Technology*, 184 F3.d 1339, 51 USPQ2d 1385 (Fed. Cir. 1999). Recognition of need and difficulties encountered by those skilled in the field are classical indicia of unobviousness. *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988).

Applicants have provided objective evidence (1) to show the pharmaceutical and medical industries failure to recognize the need for a single dosage unit as a means to enhance patient compliance to cardiovascular treatment regimens incorporating beta-blockers and platelet inhibitors while the industry recognized that compliance problems exist, (2) to show the knowledge level of one of ordinary skill in the art, and (3) to show the failure of existing modes of enhancing patient compliance and under-utilization of cardiovascular medications.

Not only does Applicants' invention represent an attempt to provide a prophylactic therapy in a single dosage unit to address the above-mentioned problems,

but Applicants' invention also attempts to improve upon the under-utilization of these specific medications, namely beta-blockers and platelet inhibitors.

Furthermore, the importance of platelet inhibitors (particularly aspirin) may be trivialized by lay individuals because of their familiarity. Some individuals instructed to take both a prescription medication and aspirin presume that the prescription is more potent. Consequently, they fail to adhere to taking aspirin. A previously submitted Exhibit 1 (JR Knight, J Clin Pharm Ther, 1991) provides evidence of the compliance problem, particularly when one medication is prescribed and the other is an over-the-counter product that is perceived as a symptomatic drug. Exhibit 1 described an abstract of a study of knowledgeable non-compliance with prescribed drugs in elderly subjects, a study with particular reference to non-steroidal anti-inflammatory and antidepressant drugs. The study involved taking one of the above drugs, and at least one other prophylactic or symptomatic drug. Non-steroidal anti-inflammatory drugs and antidepressant drugs are commonly regarded as symptomatic only and knowledgeable non-compliance is consequently high. They are also regarded as less important than drugs which produce no immediate relief of symptoms but which the patient recognizes as needing to be taken regularly to maintain health.

Applicants recognized the problems of achieving compliance, which includes the inconvenience of taking multiple dosage units over a long period of time, the lack of immediately noticeable beneficial effects, trivialization of common medications such as aspirin, and inconvenience of the requirement to obtain some medications by

prescription and some over-the-counter. (Applicants' Disclosure: Page 3, lines 16-24). Applicants recognized that many of the above mentioned problems can be ameliorated by incorporating the desired beta-adrenergic blocking agents and antagonists of platelet function into a single dosage unit. (Applicants' Disclosure: Page 3, lines 25-26).

Applicants particularly note that the problems of trivialization and non-compliance with aspirin and the requirement to purchase it over-the-counter are ameliorated by combining aspirin with a prescription medication such as beta-adrenergic blockers.

Under-utilization is clearly a concern of the medical profession. Particularly, health plan organizations are continually looking for effective ways to improve health outcomes and lower costs.

Applicants further submit new evidence that the problems still exist in the medical field. Exhibit 6, submitted herewith, is a study/investigation by Vittinghoff et al. entitled "Risk Factors and Secondary Prevention in Women with Heart Disease: The Heart and Estrogen/progestin Replacement Study", Annals of Internal Medicine, Vol. 138, No. 2, January 21, 2003, pages 81-89. This recent study further concludes that women with coronary disease are at high risk for myocardial infarction or death from coronary heart disease even in the absence of other risk factors, and their risk increases up to six-fold when many risk factors are present. Established drugs for secondary prevention, including aspirin, beta-blockers, and lipid lowering agents are underused in these women, especially those at higher risk. Exhibit 7, submitted herewith, is an editorial entitled "Secondary Prevention of Coronary Heart Disease in

Women: A Call to Action", Annals of Internal Medicine, Vol. 138, No. 2, January 21, 2003, pages 150-151. This article discusses the findings in the Vittinghoff et al. analysis (an alarming underutilization of proven therapies) and the consistent results of studies showing that the use of postmenopausal hormones for prevention or treatment of coronary heart disease in women actually increased coronary heart disease events in the first year of treatment and increased stroke and venous thromboembolic events. The article further discloses that despite clear indications for these therapies, women with more risk factors, and hence more potential benefit, were less likely than those with no risk factors to receive aspirin or other antiplatelet drugs or lipid-lowering therapy. Consequently, the article issues a call to action to implement tools to prevent coronary heart disease events in women.

Applicants also previously provided an Exhibit 2, which is an earlier study/investigation by McCormick et al. entitled "Use of aspirin, beta-blockers and lipid lowering medications before recurrent acute myocardial infarction: Missed opportunities for prevention?", Arch Intern Med, Vol 15, March 22, 1999, pages 561-567. This study addresses the concern that aspirin, beta-blockers and lipid lowering medications are under utilized.

An Exhibit 3 was also previously submitted in support of patentability of Applicants' invention. Exhibit 3 is a report from Hedis 2000, a publication that reports upon the quality of health care in the United States. It states that only 10% of MCOs (managed care organizations) had an acceptable rate of beta-blocker treatment after a

heart attack. The report concluded that if the remaining organizations that were studied performed similarly, more than 2000 cardiac deaths and tens of millions of dollars would be reduced annually.

In still another submission, Applicants refer the Office to Applicants' prior Exhibit 4 submission, which is an abstract from the Journal of the American Geriatric Society (1999) on the underutilization of aspirin in older patients with prior myocardial infarction at the time of admission to a nursing home. The conclusion is that there is a marked underutilization of aspirin in the treatment of older patients with documented prior myocardial infarction at the time of admission.

In yet another prior submission, Applicants' Exhibit 5 was an abstract from the Canadian Journal of Cardiology (1999) on the under use of acetylsalicylic acid (aspirin) in individuals with myocardial infarction, ischemic heart disease or stroke. It concludes that acetylsalicylic acid appears to be underused in those at high risk for future vascular events.

Further, the solutions to problems with compliance and under-utilization of helpful medications for cardiovascular treatments are elusive, and have troubled the healthcare industry for a long time. The industry continues to struggle to find answers to these perplexing questions. The healthcare industry's focus is now and has always been to educate physicians and patients, not to providing novel means for achieving better patient compliance and utilization results. Dr. Gurwitz's declaration is evidence that the healthcare industry's approach is to educate physicians and patients.

Similarly, this problem has been overlooked by the pharmaceutical industry despite considerable motivation, i.e. increased sales, to increase usage of medication.

Applicants submit that without some teaching or suggestion in the prior art that addresses solutions to the problem of the failure of patients to receive specific cardiovascular treatments and to improve compliance, the present invention would be obvious only in hindsight.

It is clear from Applicants' disclosure that Applicants' invention is a combination of old elements. In determining obviousness, "the inquiry is not whether each element existed in the prior art, but whether the prior art made obvious the invention as a whole for which patentability is claimed." Hartness International, Inc. v. Simplimatic Engineering Co., 819 F.2d 1100, 2 USPQ2d 1826 (Fed. Cir. 1987). If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit one to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. Such an approach would be 'an illogical and inappropriate process by which to determine patentability.' In re Rouffet, 149 F.3d 1350, 47 USPQ2d 1453 (Fed. Cir. 1998). When the patented invention is made by combining known components to achieve the new system, the prior art must provide a suggestion or motivation to make such a combination. Heidelberger Druckmaschinen AG v. Hantscho Commercial Prods., Inc., 21 F.3d 1068 (Fed. Cir. 1994). It is insufficient that the prior

art shows similar components, unless it also contains some teaching, suggestion, or incentive for arriving at the claimed structure. Northern Telecom, Inc. v. Datapoint Corp., 908 F.2d 931 (Fed. Cir. 1990). There is no basis for concluding that an invention would have been obvious solely because it is a combination of elements that were known in the art at the time of the invention. Smiths Industries Medical Systems, Inc. v. Vital Signs, Inc., 50 USPQ2d 1641, *superseded on rehearing*, 183 F.3d 1347, 51 USPQ2d 1415 (Fed. Cir. 1999).

It is clear that when Applicants' invention is viewed as a whole the prior art contains no suggestion to combine Applicants' cardiovascular treatment medications into a single dosage unit. Where Applicants' components are similar to those components shown and disclosed in the prior art, the law requires that the prior art also contain some teaching, suggestion or incentive for arriving at Applicants' claimed structure. The Office has failed to provide this showing. The Office states that one of ordinary skill in the art would have been motivated to combine the medications into a single dosage unit because they are known to be useful for the same purpose. The Office relies on its conclusion based on In re Kerkhoven, 205 USPQ 1069 (CCPA 1980).

In accordance with the more recent rulings of the Federal Circuit, the Office must point to some teaching, suggestion or incentive in the cited prior art for arriving at the claimed structure. The Office has failed to do this. On the other hand, Applicants have provided evidence of noncompliance problems, the under-utilization of medications and

the Declaration of Dr. Gurwitz as to the healthcare industries' struggles to find answers to these perplexing questions.

In light of the above arguments, Applicants respectfully submit that Claims 1-7, 9-11 and 13-17 of the present application contain allowable subject matter and that the 35 USC §103(a) rejections have been successfully traversed.

Applicants believe that all of the pending claims should now be in condition for allowance. Early and favorable action is respectfully requested.

The Examiner is invited to telephone the undersigned, Applicant's attorney of record, to facilitate advancement of the present application.

Respectfully submitted,

Dated: 6/9/03

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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, PO Box 1450, Alexandria, VA 22313-1450, on:

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Robert R. Deleault

Annals of Internal Medicine | ARTICLE

Risk Factors and Secondary Prevention in Women with Heart Disease: The Heart and Estrogen/progestin Replacement Study

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Background: Risk factors for coronary heart disease events have most commonly been evaluated in healthy men.

Objective: To assess risk factors, event rates, and use of secondary prevention treatments in women with preexisting coronary disease.

Design: A prospective cohort of clinical trial participants.

Setting: 20 U.S. clinical centers.

Participants: 2763 postmenopausal women with known coronary disease in the Heart and Estrogen/progestin Replacement Study (HERS).

Measurements: Myocardial infarction or death from coronary heart disease.

Results: On multivariable analysis, the researchers found 11 risk factors: 6 noted by history (nonwhite ethnicity, lack of exercise, treated diabetes, angina, congestive heart failure, and more than one previous myocardial infarction) and 5 that were measured (blood pressure, low-density lipoprotein cholesterol level, high-density lipoprotein cholesterol level, lipoprotein(a) level, and creatinine clearance). The annual rate of coronary events was 1.3% (95% CI, 0.7% to 2.5%) in women with no risk factors and 8.7% (CI, 7.1% to 10.8%) in women with five or more risk factors (a sixfold increase). At entry into HERS, 83% of participants were receiving aspirin or other antiplatelet agents, 33% were receiving β-blockers, 18% were receiving angiotensin-converting enzyme inhibitors, and 53% were receiving lipid-lowering drugs. Women with more risk factors were less likely to be taking aspirin ($P <$ 0.001) and lipid-lowering drugs ($P =$ 0.006).

Conclusions: Women with coronary disease are at high risk for myocardial infarction or death from coronary heart disease even in the absence of other risk factors, and their risk increases up to sixfold when many risk factors are present. Established drugs for secondary prevention, including aspirin, β-blockers, and lipid-lowering agents, are underused in these women, especially those at highest risk.

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For author affiliations, see end of text.
See editorial comment on pp 150-151.

Coronary heart disease (CHD) is the leading cause of death in women. The major independent risk factors that predict CHD onset in healthy women are similar to those identified by epidemiologic studies of healthy men (1–7). A recent report described six independent risk factors—age, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol levels, high blood pressure, diabetes mellitus, and smoking—that were strongly associated with risk for a first CHD event in both men and women (8). However, the strength of the association of certain risk factors with CHD events may vary by sex (9) as well as age. Diabetes may be a stronger risk factor in women than in men (7); among older women, HDL cholesterol level may be a relatively strong risk factor and LDL cholesterol level a relatively weak one (6).

In the period immediately after myocardial infarction (MI), studies of mostly male samples have found that persistent ischemia, impaired left ventricular systolic function, and ventricular arrhythmias are the major determinants of subsequent MI and death (10–13). In the Coronary Drug Project study of men with a history of heart attack, electrocardiographic abnormalities and heart failure were stronger predictors than the atherosclerosis risk factors identified in primary prevention settings (14). However, the risk factors for coronary events among women with recognized but stable coronary disease are mostly unknown. Better understanding of these factors could improve secondary prevention in this large and high-risk group.

The Heart and Estrogen/progestin Replacement Study (HERS) was a randomized clinical trial of estrogen plus progestin for prevention of CHD events in women with coronary disease (15). Overall, no significant differences were noted between the hormone and placebo groups in CHD events; trends of more CHD events with therapy in year 1 were offset by fewer such outcomes during years 4 and 5. The trial collected extensive data on CHD risk factors and medication use and performed exhaustive outcome ascertainment procedures, with complete mortality follow-up. Therefore, HERS offers a unique opportunity to assess the long-term effect of coronary risk factors and use of recommended treatments in women with established coronary disease.

Methods

Participants

Participants in HERS were postmenopausal women who were younger than 80 years of age, had not had a hysterectomy, and had known coronary artery disease (MI, coronary artery bypass surgery, percutaneous transluminal coronary angioplasty, or angiographic evidence of ≥50% narrowing of one or more major coronary arteries). Women were excluded if they had had a coronary event

Context

Risk factors for recurrent events among women with known coronary disease and whether these women commonly receive secondary prevention treatments are mostly unknown.

Contribution

This large cohort study showed that 11 different factors, including several previous infarctions, renal dysfunction, diabetes, angina, heart failure, and uncontrolled hypertension, predicted up to a sixfold increased rate of coronary disease events in postmenopausal women with preexisting coronary disease. Despite high risks, half or fewer women were taking β-blockers, angiotensin-converting enzyme inhibitors, or cholesterol-lowering drugs.

Implications

Clinicians can identify women who have high risks for recurrent coronary events and should promote greater use of secondary prevention treatments for them.

–The Editors

within the 6 months before randomization, had a serum triglyceride level greater than 3.39 mmol/L (300 mg/dL), had used hormones within 3 months, or had a history of conditions that would contraindicate estrogen therapy (16). Participants in HERS were randomly assigned within clinical centers to 0.625 mg of conjugated equine estrogen plus 2.5 mg of medroxyprogesterone acetate in one tablet daily (n = 1380) or a placebo of identical appearance (n = 1383). The institutional review boards at the coordinating center and each of the 20 HERS clinical centers approved the protocol, and all participants provided written informed consent.

Predictors

In the baseline interview, information was obtained by self-report on demographic characteristics, behavioral risk factors, and medical history. Among women who reported ever having smoked at least 100 cigarettes, years of smoking, average cigarettes per day, and current smoking were ascertained. Alcohol use in the past 30 days was assessed for frequency and usual numbers of drinks per occasion. Exercise was measured as participation in a "regular exercise program such as cardiac rehabilitation or aerobics" or walking at least occasionally "for exercise more than 10 minutes at a time." Use of aspirin, β-blockers, lipid-lowering medications (statins, niacin, fibrates, bile acid–binding resins, and probucol), angiotensin-converting enzyme (ACE) inhibitors, calcium antagonists, and folate or vitamin B was assessed by self-report.

In the baseline physical examination, blood pressure, waist-to-hip ratio, and body mass index were measured. A physician assessed history and symptoms of heart failure (jugular venous distension, third heart sound, significant murmurs, pulmonary rales, and peripheral edema). High blood pressure was defined as systolic blood pressure greater than or equal to 140 mm Hg or diastolic blood pressure greater than or equal to 90 mm Hg, according to the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (17). Angina was defined as self-report of chest discomfort in the previous 4 weeks during exercise, emotion, or sexual activity. Serum specimens were obtained, and a centralized laboratory measured fasting levels of LDL cholesterol, HDL cholesterol, lipoprotein(a), triglycerides, glucose, and creatinine (15, 16). Creatinine clearance was estimated by using the Cockcroft–Gault equation (18, 19).

Outcomes

The primary HERS outcome was CHD events, defined as nonfatal MI or CHD death. Suspected outcome events were reported within 24 hours to the coordinating center and were systematically assessed every 4 months at the follow-up contacts. An independent morbidity and mortality subcommittee that was blinded to treatment assignment adjudicated all deaths and suspected outcome events. Nonfatal MI was diagnosed by using an algorithm based on ischemic symptoms, electrocardiographic abnormalities, and elevated cardiac enzyme levels (16). Death from CHD included fatal documented MI, sudden death within 1 hour of symptom onset, unobserved death that occurred out of the hospital in the absence of other known causes, or death due to a coronary revascularization procedure or congestive heart failure. The date of each event was determined from the documentation obtained by the clinical centers. The total number of events reported here is slightly larger than that published in the primary HERS results (15) because of subsequent adjudications (20).

Statistical Analyses

We used multivariable Cox proportional hazards models to assess the associations between risk factors and CHD events. These models were stratified by clinical center to account for potential clustering. Waist-to-hip ratio and LDL and HDL cholesterol levels were modeled as continuous variables, but lipoprotein(a) level was dichotomized at the median and creatinine clearance was dichotomized at 0.66 mL/s (40 mL/min) to reflect the nonlinear responses we have reported elsewhere (19, 21). We used an indicator for any alcohol use, since almost all of the 39% of HERS women who reported alcohol use were light or moderate drinkers. Exercise was modeled by an indicator for participation in an exercise program or walking for exercise for more than 10 minutes.

The multivariable model includes previously identified risk factors that were significant ($P \leq 0.20$) in unadjusted models and were not judged redundant on substantive grounds. Body mass index was excluded because it was clearly nonsignificant after adjustment ($P > 0.2$) and was also highly correlated with waist-to-hip ratio, which was

the stronger predictor in unadjusted analysis. Similarly, triglyceride levels were excluded because of their strong negative correlation with HDL cholesterol levels, which in our judgment were more likely to be causal. We also controlled for use of aspirin, statins, other lipid-lowering medications, diuretics, β-blockers, ACE inhibitors, calcium antagonists, and folate or vitamin B. The effect of assignment to hormone therapy was modeled separately for each year of follow-up, as in the post hoc analysis of HERS (15).

Interactions between risk factors and relevant treatments were also examined. Specifically, we compared hazard rates among patients with diagnosed diabetes who reported use of insulin or oral hypoglycemic agents with rates in the combined group of diabetic persons not using these medications and women with fasting glucose levels greater than 6.94 mmol/L (>125 mg/dL) but no history of diabetes diagnosis. Likewise, we compared estimates for LDL and HDL cholesterol levels stratified by use of any lipid-lowering medication or assignment to hormone therapy; for lipoprotein(a) level, stratified by assignment to hormone therapy; for high blood pressure on examination, stratified by use of at least one antihypertensive medication; for heart failure and creatinine clearance less than or equal to 0.66 mL/s (≤40 mL/min), stratified by use of ACE inhibitors; and for more than one previous MI and angina, stratified by use of any indicated medications. The final model includes interactions that were significant at a P value less than or equal to 0.2.

We used residuals to assess overall model fit, validity of the proportional hazards assumption, and linearity of associations with continuous predictors. The study lacked power to examine interactions between clinical center and potential risk factors. We tested the assumption of noninformative censoring by considering the two extremes of the possible outcomes for the 60 women lost to clinical follow-up before the end of HERS, first as events at the time of censoring, then as observations censored at the longest observed follow-up time.

The average annual rate of CHD events was estimated overall and for groups defined by number of risk factors present among the 11 predictors identified in the multivariable Cox model. To evaluate this number, LDL and HDL cholesterol levels were dichotomized at standard cutpoints for elevated risk. Within these groups, we tabulated use of aspirin and other antiplatelet agents, β-blockers, ACE inhibitors, and lipid-lowering therapy, both at baseline and at the end of the study. We also tabulated the proportions of women with various risk factors who were receiving indicated treatments. Because the third report of the National Cholesterol Education Program has only recently been published (22), the denominator for lipid-lowering medication use excluded nonusers with LDL cholesterol levels less than 3.4 mmol/L (<130 mg/dL), which was the criterion for initiating therapy among women with coronary disease in the second report of the National Cholesterol Education Program (NCEP II) (23). Similarly, the denominator for use of aspirin or other antiplatelet agents excluded women using warfarin. All analyses were performed by using SAS, version 8.02 (SAS Institute, Inc., Cary, North Carolina).

Role of the Funding Source

Wyeth-Ayerst Research funded the HERS clinical trial, implemented data collection, and reviewed the manuscript before submission for publication. The investigators were not required by contract to make any revisions suggested by Wyeth-Ayerst.

RESULTS

During an average of 4.1 years of follow-up in 1993 to 1998, 361 of 2763 women in HERS had nonfatal MI or died of CHD. Of the 232 women with nonfatal MI, 24 subsequently died of CHD. The 129 CHD deaths included 35 fatal MIs, 38 sudden deaths, 16 deaths from congestive heart failure or pulmonary edema, 24 deaths that were unwitnessed or occurred during sleep, and 16 deaths from other or unclassified CHD causes.

Unadjusted Analyses

Nonwhite women were twice as likely as white women to have a CHD event (**Table 1**). Both alcohol use and regular exercise were associated with lower event rates. Treated diabetes, congestive heart failure, a history of at least two MIs, and angina by self-report were associated with increased event rates. Higher blood pressure, waist-to-hip ratio, LDL cholesterol level, and triglyceride levels, as well as lower HDL cholesterol level and creatinine clearance (≤0.66 mL/s [≤40 mL/min]) were associated with CHD events.

Adjusted Analyses

In the multivariable model (**Table 2**), increased rates of CHD events were associated with diabetes (among those taking insulin or oral hypoglycemic agents), high blood pressure, at least two previous MIs, heart failure, angina, creatinine clearance less than or equal to 0.66 mL/s (≤40 mL/min), lipoprotein(a) level at least 0.90 mmol/L (≥25.3 mg/dL) among women assigned to placebo, lack of exercise, and African-American ethnicity. We also found probable associations with higher LDL and lower HDL cholesterol levels (P = 0.06 for both). Weaker evidence was observed for increased rates among Latin-American women and women of other nonwhite ethnicity, older women, and current smokers. The findings were similar if weak predictors (including former smoking, untreated diabetes, lipoprotein(a) level among women assigned to hormone therapy, and previous percutaneous transluminal coronary angioplasty) were excluded from the model, or if we used a quantitative measure of alcohol use. The estimate for HDL cholesterol level was attenuated if triglyceride level was added to the model shown in **Table 2**, but triglyceride level is the weaker predictor and was nonsignificant. Furthermore, triglyceride level was not statistically significant in a

Table 1. **Risk Factors for Coronary Heart Disease Events***

Risk Factor	Participants without CHD Events (*n* = 2402)	Participants with CHD Events (*n* = 361)	Relative Hazard (95% CI)†	*P* Value
Demographic characteristics				
Mean age at randomization ± SD, *y*	66.6 ± 6.6	66.9 ± 6.7	1.11 (0.95–1.30)	0.2
Ethnicity, %				
African American	7	14	2.05 (1.52–2.77)	<0.001
Latin American	2	3	1.61 (0.86–3.03)	0.14
Other nonwhite	1	2	1.87 (0.93–3.78)	0.08
Health-related behaviors, %				
Smoking				
Current	13	15	1.24 (0.93–1.65)	0.14
Former	50	44	0.84 (0.67–1.06)	0.14
Any alcohol consumption	40	31	0.67 (0.53–0.83)	<0.001
Exercise‡	66	53	0.60 (0.49–0.74)	<0.001
Medical conditions, %§				
Diabetes				
Receiving insulin or oral hypoglycemic agents	17	29	2.01 (1.59–2.54)	<0.001
Other	8	8	1.12 (0.76–1.66)	>0.2
≥2 previous myocardial infarctions	5	9	1.88 (1.30–2.72)	<0.001
Previous PTCA	44	40	0.85 (0.69–1.05)	0.14
Angina	25	36	1.66 (1.34–2.05)	<0.001
Physical examination				
Mean BMI ± SD, *kg/m²*	28.5 ± 5.4	29.1 ± 6.1	1.09 (0.98–1.20)	0.10
Mean waist-to-hip ratio ± SD	0.87 ± 0.08	0.88 ± 0.08	1.15 (1.04–1.28)	0.007
High blood pressure, %‖	37	49	1.61 (1.31–1.98)	<0.001
History or symptoms of CHF, %	11	19	1.76 (1.35–2.28)	<0.001
Laboratory results				
Mean LDL cholesterol level ± SD, *mmol/L (mg/dL)*	3.74 ± 0.97 (144 ± 38)	3.90 ± 1.02 (151 ± 40)	1.15 (1.05–1.27)	0.004
Mean HDL cholesterol level ± SD, *mmol/L (mg/dL)*	1.31 ± 0.34 (50.6 ± 13.3)	1.25 ± 0.32 (48.3 ± 12.4)	0.85 (0.76–0.95)	0.004
Lipoprotein(a) level > 0.90 mmol/L (>25.3 mg/dL), %				
Placebo group	24	30	1.49 (1.11–2.00)	0.008
Hormone therapy group	25	25	0.97 (0.72–1.30)	>0.2
Mean triglyceride level ± SD, *mmol/L (mg/dL)*	1.87 ± 0.71 (165 ± 63)	1.96 ± 0.75 (173 ± 66)	1.14 (1.03–1.26)	0.01
Creatinine clearance ≤ 0.66 mL/s (≤40 mL/min), %	11	17	1.78 (1.35–2.34)	<0.001

* Coronary heart disease events include nonfatal myocardial infarction and death from CHD. All listed risk factors were previously identified as associated with CHD events in unadjusted analysis ($P \le 0.20$). Additional variables screened in preliminary analysis include education, marital status, living situation, heart rate, and individual signs of heart failure. BMI = body mass index; CHD = coronary heart disease; CHF = congestive heart failure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PTCA = percutaneous transluminal coronary angioplasty.
† From unadjusted Cox models. The relative hazard is per 10 years for age and per SD for BMI; waist-to-hip ratio; and LDL cholesterol, HDL cholesterol, and triglyceride levels.
‡ Defined as regular participation in an exercise program or walking for at least 10 minutes.
§ Other women with diabetes include those reporting a history of diagnosis but no medication use and women with fasting plasma glucose levels > 6.94 mmol/L (>125 mg/dL). Angina was defined by self-report as chest pain in the past 4 weeks during exercise, emotion, or sexual activity.
‖ High blood pressure is defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥90 mm Hg.

multivariable model from which HDL level was excluded. The multivariable model was determined by using data for 2740 of 2763 women (99%) with no missing covariate values and included 354 of the 361 observed events (98%). We found little evidence for violation of the proportional hazards assumption ($P > 0.2$). However, the results for HDL cholesterol level and smoking were uncertain because they were sensitive to the untestable assumption of noninformative censoring.

CHD Events and Use of Medications by Number of Risk Factors

Overall, the average annual rate of CHD events was 3.4% (95% CI, 3.1% to 3.8%) (Table 3). Half of all women had at least two risk factors. Average annual rates increased sixfold, from 1.3% among women with no risk factors to 8.7% among women with five or more risk factors ($P < 0.001$ for trend). Despite this increasing gradient, women with five or more risk factors appeared to be the least likely to receive aspirin ($P < 0.001$ for trend) and lipid-lowering therapy ($P = 0.006$ for trend). Use of β-blockers was similar across subgroups. Use of ACE inhibitors, however, increased with the number of risk factors ($P < 0.001$ for trend).

Time Trends in Secondary Prevention

We also examined use of these secondary prevention drugs at the end of the study. Use of aspirin and other antiplatelet agents had decreased slightly from 83% to 79%, and use of β-blockers was essentially unchanged (33% vs. 35%) (Table 3). Use of any lipid-lowering medication had increased from 53% to 66% among women who met NCEP II criteria; most were taking statins. The associations at baseline between number of risk factors and use of aspirin or other antiplatelet agents, ACE inhibitors, and lipid-lowering therapy persisted at the end of the study.

Use of Indicated Medications by Risk Factor

For certain risk factors, we evaluated the proportions of women using indicated medications. Only 37% of women with diagnosed heart failure and only 24% of women with creatinine clearance of 0.66 mL/s or less (≤40 mL/min) used ACE inhibitors (Table 4). Use of β-blockers and aspirin or other antiplatelet agents was similar among women with previous MI and those with angina symptoms.

Discussion

We found 11 risk factors for MI or coronary death in our cohort of women with previous coronary artery disease. Of these factors, 6 were noted by history (nonwhite ethnicity, lack of exercise, treated diabetes, angina, congestive heart failure, and more than one previous MI) and 5 were measured (blood pressure, LDL cholesterol level, HDL cholesterol level, lipoprotein(a) level, and creatinine clearance). Compared with women in primary prevention settings (8), women with no risk factors had a substantial absolute risk for nonfatal MI or CHD death. This risk was increased sixfold in women with five or more risk factors.

Two of the six conventional risk factors that were independent predictors of CHD events in healthy middle-aged women in the Framingham Study (8) were not risk factors in HERS. The nonsignificant relative hazard estimates for age and smoking in our study appear to differ from findings in other samples of persons with coronary disease (14, 24), but wide confidence intervals suggest that the differences between studies would not be statistically significant. In addition, because smoking was not prevalent in HERS, we had less power to detect a clinically relevant association. The relative hazards for diabetes, high blood pressure, LDL cholesterol level, and HDL cholesterol level in women in HERS, while statistically significant, were somewhat weaker than those estimated in women without CHD (6, 8) and resemble findings in men with previous coronary disease (14). The excess event rates associated with these risk factors are greater than in primary prevention because the baseline rate in the secondary prevention setting is substantially higher (25).

Differing patterns of risk factors in HERS compared with primary prevention settings may result from differences in age or in the presence of established coronary disease. Participants in HERS were on average 67 years of age, and some risk factors, notably serum cholesterol level and tobacco use, may become less predictive of CHD events as age increases (26, 27). In addition, determinants of atherosclerosis, which play a central role in predicting CHD risk in patients without manifest coronary disease, may be less important than measures of recurrent ischemia, myocardial function, and arrhythmia in patients in whom coronary disease has been established (10–13, 28).

Although all participants in HERS had established coronary artery disease, only about half had had an MI before enrollment. Twenty-six percent reported angina, and 12% had had heart failure. We found that those with two or more previous MIs and those with angina had substantially greater risk for subsequent CHD events. Congestive heart failure was also independently associated with CHD events. Because women with severe symptoms of heart failure were excluded from HERS, we may have underestimated the association of heart failure with coronary events in women with known coronary disease.

Table 2. **Multivariate Cox Regression Analyses of Risk Factors for Coronary Heart Disease Events***

Risk Factor	Relative Hazard (95% CI)	P Value
Well supported by overall evidence, including previous findings		
Ethnicity		
African American	1.44 (1.02–2.04)	0.04
Latin American	1.92 (0.95–3.91)	0.07
Other nonwhite	1.87 (0.89–3.91)	0.10
Exercise program or walking for ≥10 minutes	0.80 (0.64–1.00)	0.05
High blood pressure on examination†	1.55 (1.16–2.07)	0.003
Diabetes treated with insulin or oral hypoglycemic agents‡	1.51 (1.16–1.98)	0.001
LDL cholesterol level (per SD)	1.10 (1.00–1.22)	0.06
HDL cholesterol level (per SD)	0.89 (0.79–1.01)	0.06
Lipoprotein(a) level > 0.90 mmol/L (>25.3 mg/dL) in the placebo group§	1.44 (1.06–1.96)	0.02
Creatinine clearance ≤ 0.66 mL/s (≤40 mL/min)	1.56 (1.16–2.11)	0.004
≥2 previous myocardial infarctions	1.79 (1.22–2.62)	0.003
History or symptoms of CHF	1.33 (1.00–1.78)	0.05
Angina‖	1.49 (1.18–1.87)	<0.001
Other		
Age (per 10 years)	1.13 (0.94–1.37)	0.19
Smoking		
Current	1.30 (0.92–1.84)	0.13
Past	0.99 (0.78–1.26)	>0.2
Any alcohol use	0.97 (0.75–1.25)	>0.2
Waist-to-hip ratio (per 0.10 unit)	1.03 (0.89–1.20)	>0.2
Other diabetes¶	0.91 (0.60–1.36)	>0.2
History of hypertension with normal blood pressure	1.18 (0.87–1.62)	>0.2
Lipoprotein(a) level > 0.90 mmol/L (>25.3 mg/dL) in the hormone therapy group**	0.97 (0.71–1.32)	>0.2
Previous PTCA	0.94 (0.76–1.18)	>0.2

* Coronary heart disease events include nonfatal myocardial infarction and death from coronary heart disease. Estimates are adjusted for assignment to hormone therapy and for use of statins, other lipid-lowering medications, aspirin, angiotensin-converting enzyme inhibitors, β-blockers, calcium antagonists, diuretics, and folate or vitamin B. The factors in Table 1 were considered for inclusion in the multivariable model; only body mass index and triglyceride level were excluded (see Methods). CHF = congestive heart failure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PTCA = percutaneous coronary angioplasty.
† High blood pressure is defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥90 mm Hg.
‡ The reference group is women who did not report a history of diagnosis and had a baseline glucose level ≤ 6.94 mmol/L (≤125 mg/dL).
§ The reference group is women assigned to placebo who had a lipoprotein(a) level ≤ 0.90 mmol/L (≤25.3 mg/dL).
‖ Angina is defined by self-report as chest pain in the past 4 weeks during exercise, emotion, or sexual activity.
¶ Includes women reporting a history of diagnosis but no medication use and those with fasting plasma glucose levels > 6.94 mmol/L (>125 mg/dL). The reference group is women who did not report a history of diagnosis and had a baseline glucose level ≤ 6.94 mmol/L (≤125 mg/dL).
** The reference group is women assigned to hormone therapy who had a lipoprotein(a) level at or below the median.

Table 3. **Risk for Coronary Heart Disease Events and Use of Preventive Medications according to Number of Risk Factors***

Risk Factors†	Women	Annual CHD Event (95% CI)‡	Women Taking Aspirin and Other Antiplatelet Agents§		Women Taking β-Blockers		Women Taking ACE Inhibitors		Women Taking Lipid-Lowering Drugs‖	
			Baseline	End of the Study	Baseline	End of the Study	Baseline	End of the Study	Baseline	End of the Study
	n (%)	←				%				→
0	164 (6)	1.3 (0.7–2.5)	94	85	36	35	10	12	58	72
1	540 (20)	2.4 (1.9–3.2)	89	82	30	35	12	22	53	68
2	722 (26)	2.1 (1.7–2.7)	84	80	31	34	15	23	54	62
3	656 (24)	3.3 (2.6–4.1)	82	77	32	36	17	28	51	62
4	398 (14)	5.1 (4.1–6.4)	80	78	34	33	21	32	45	55
≥5	283 (10)	8.7 (7.1–10.8)	77	76	37	37	29	42	48	59
Overall	2763 (100)	3.4 (3.1–3.8)	83	79	33	35	18	28	53	66

* P value for trend in risk by number of risk factors is <0.001. ACE = angiotensin-converting enzyme; CHD = coronary heart disease.
† Number of risk factors includes lack of exercise, systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg, diabetes, low-density lipoprotein cholesterol level > 3.4 mmol/L (>130 mg/dL), high-density lipoprotein cholesterol level < 0.91 mmol/L (<35 mg/dL), lipoprotein(a) level > 0.90 mmol/L (>25.3 mg/dL), nonwhite ethnicity, creatinine clearance ≤ 0.66 mL/s (≤40 mL/min), ≥2 previous myocardial infarctions, angina, and heart failure. These are the 11 risk factors identified as important in the multivariable model (Table 2). To evaluate the number of risk factors, low-density lipoprotein cholesterol level and high-density lipoprotein cholesterol level were dichotomized at established cut-points for elevated CHD risk.
‡ 95% CIs were computed under a Poisson assumption.
§ For aspirin and antiplatelet agents, the denominators excluded women using warfarin.
‖ For lipid-lowering medications, the number of risk factors does not include levels of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, or lipoprotein(a). Denominators excluded nonusers with normal lipid levels.

Whereas symptoms of angina and heart failure were associated with increased event rates, regular exercise was associated with decreased CHD events in HERS. This finding could represent the benefits of physical activity among women with CHD or simply reflect the greater propensity of healthy women to exercise. In contrast, we did not find obesity, defined either by body mass index or waist-to-hip ratio, to be a significant independent risk factor in HERS after adjustment for exercise and other covariates. However, because of the significant unadjusted association between obesity and CHD events and because it is a modifiable risk factor for high blood pressure and diabetes, obesity is an appropriate target for secondary prevention efforts (29).

We identified two risk factors in HERS that are not as well known: reduced renal function and elevated lipoprotein(a) levels. Moderate renal insufficiency has been increasingly recognized as an independent predictor of cardiovascular events and death, but the mechanisms for the association are not clear (6, 21, 30, 31). Renal insufficiency has been linked both to the incidence of heart failure and to poor survival after heart failure (32, 33). Prevalence of moderate renal insufficiency, as defined by estimated creatinine clearance less than or equal to 0.66 mL/s (≤40

Table 4. **Use of Indicated Medications by Risk Factor Status***

Risk Factor	Indicated Medication	All Women with the Risk Factor	Women with the Risk Factor Who Were Receiving the Indicated Medication
		n (%)	
LDL cholesterol level ≥ 3.4 mmol/L (≥130 mg/dL)	Any lipid-lowering therapy	2355 (85)†	1287 (55)
	Statins		1004 (43)
History or symptoms of CHF	ACE inhibitors	345 (12)	128 (37)
Any previous MI	β-blockers	1409 (51)	477 (34)
	Aspirin or other antiplatelet agent		1134 (80)
≥2 previous MIs	β-blockers	143 (5)	44 (31)
	Aspirin or other antiplatelet agent		109 (76)
Angina without history of MI	β-blockers	383 (14)	157 (41)
	Aspirin or other antiplatelet agent		298 (78)
Creatinine clearance ≤ 0.66 mL/s (≤40 mL/min)	ACE inhibitors	323 (12)	78 (24)

* ACE = angiotensin-converting enzyme; CHF = congestive heart failure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MI = myocardial infarction.
† Includes women with normal LDL cholesterol level who were receiving lipid-lowering therapy.

mL/min), was 13% in the HERS cohort. This prevalence increases with age, making moderate renal insufficiency a risk factor of greater importance in this sample than in younger women (19).

Lipoprotein(a) levels were also a statistically significant risk factor, but only in the placebo group. The absence of an association between lipoprotein(a) level and CHD events in the active treatment group can probably be explained by the reduction in lipoprotein(a) levels caused by hormone therapy. We have previously shown that for women in HERS, reductions in lipoprotein(a) levels were independently associated with reduced rates of CHD events (21). Lipoprotein(a) level may prove to be an important consideration in secondary prevention efforts.

Despite the high CHD risk among HERS participants, the use of medications for secondary prevention was inadequate. In women with heart disease, treatment with aspirin, β-blockers, and lipid-lowering agents is one of the cornerstones of secondary prevention (22, 29, 34). One of the most important findings in HERS was the substantial underuse of these proven therapies (35, 36). Although most women in HERS were taking aspirin at enrollment, only one third were treated with β-blockers and only half of those who met NCEP II criteria for lipid-lowering therapy were using statins or other lipid-lowering treatments. Of concern, the women who had the greatest risk for CHD events in HERS were the least likely to be treated with aspirin or lipid-lowering medications. Furthermore, during the 4-year follow-up, use of β-blockers remained unchanged and use of aspirin and other antiplatelet agents decreased. Although use of statins increased during HERS, only two thirds of participants who met 1993 NCEP II criteria for treatment were taking lipid-lowering agents at the end of the study. Similarly low rates of utilization of these medications, as well as of other preventive interventions (ACE inhibitors, blood pressure and weight control, diet, exercise, and smoking cessation), have been observed in other clinical settings (37–44). In addition, women often receive less treatment than men (45–47). Proactive, targeted interventions should be developed to improve utilization of these preventive therapies (48).

The primary limitation of our study is that we examined voluntary participants in a secondary prevention trial. Our sample therefore may differ from the general population of women with coronary artery disease. Clinical trial participants tend to be healthier and more health conscious and therefore may be less in need of and more likely to engage in preventive behaviors. In addition, the enrollment criteria for HERS excluded the most infirm candidates, as evidenced by the lower-than-expected event rates (15). As a result, the significant associations we detected with dichotomous risk factors, including hypertension, diabetes, heart failure, and renal insufficiency, could represent underestimates. However, only 6% of women screened were excluded because of high serum levels of triglycerides, aspartate aminotransferase, or glucose (16).

The risk factor classifications that we considered important were to some extent data driven. This may inflate the type I error rates or the likelihood of mistakenly concluding that the observed associations are important. Our conclusion that LDL and HDL cholesterol levels are important risk factors was based on our interpretation of a multivariate *P* value of 0.06 in the context of information from other studies; other interpretations may also be valid. A further limitation is that the predictor variables measured in HERS did not include diagnostic tests, such as echocardiography and exercise testing, that might better predict clinical outcomes among women with coronary artery disease than risk factors for atherosclerosis. We also did not have good information on contraindications to medications, which may mean that our estimates of appropriate utilization are too low.

In conclusion, we used multivariable analysis to identify 11 easily assessed characteristics that predicted up to a sixfold increase in CHD events in a large sample of women who were already at high risk because they had coronary disease. This set of risk factors differs from those that have been established in primary prevention settings. In addition, we found substantial underuse of preventive treatments that have been established as beneficial, notably aspirin, β-blockers, and statins.

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Sunday at the Nursing Home

My mother is shrinking.
When I was little she was huge,
a mountain of a woman,
her peak covered by clouds of curls.
I craned my neck to the skies
just to see her smile.
Getting dressed, naked,
putting on her bra, she loomed:
Enormous. Majestic.
Now she is mostly flat, lying
on strange sheets:
More a prairie with dried grass
I flex my neck down to view.
My little boy watches me, too.
It's impossible not to notice
everyday
I get
smaller.

Bonnie Salomon, MD
Lake Forest, IL 60045

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Exhibit 7

Secondary Prevention of Coronary Heart Disease in Women: A Call to Action

On the basis of extensive mechanistic evidence from in vitro and animal studies and clinical evidence from observational studies, it was predicted that postmenopausal hormone replacement therapy would protect women from coronary heart disease (CHD) events. However, the results of randomized, controlled trials available to date have not supported this prediction (1–3). In fact, the studies have shown evidence of harm—increased CHD events in the first year of treatment and increased stroke and venous thromboembolic events. Although these trials have acknowledged limitations, including use of only a single hormone preparation and participation of older women after many hormone-free years (a practice not usually followed in clinical care), the consistency of these results clearly does not support the use of postmenopausal hormones for prevention or treatment of CHD in women (4).

This leaves us with a growing population of middle-aged and elderly women who have lost the cardiovascular protection of their younger years and for whom unique sex-specific preventive and treatment strategies do not exist. Assessing risk and using effective preventive strategies in these women is critical: CHD is by far the leading cause of death, and deaths due to cardiovascular disease are increasing in American women despite advances in prevention and therapy (5). Women have higher mortality rates and are less likely to receive standard interventions after myocardial infarction than men (6). The prevalence of obesity and type 2 diabetes is increasing, particularly among African-American women, which also increases CHD risk (7, 8). Historical improvements in smoking prevention and cessation, dyslipidemia treatment, and hypertension control have stagnated, further adding to the problem (9). Risk factors for CHD events in persons with established CHD have largely been defined in men, leaving providers with an inadequate body of evidence on which to base secondary prevention of CHD in women.

The Heart and Estrogen/progestin Replacement Study (HERS) collected extensive data on CHD risk factors and medication use, as well as CHD outcomes in 2763 older postmenopausal women (average age, 67 years) with established CHD. These women were randomly assigned to combined conjugated estrogen plus progestin versus placebo and followed for an average of 4.1 years (1, 2). In this issue, Vittinghoff and colleagues (10) analyze data from this study to identify risk factors for myocardial infarction and CHD death and describe use of secondary prevention strategies by the participants. Using 11 variables that were significant from unadjusted models, they calculated hazard ratios with multivariable Cox proportional hazards models.

The strongest predictor (hazard ratio, 1.79 [95% CI, 1.27 to 1.62]) of subsequent events was the presence of many previous myocardial infarctions. Other robust (hazard ratio $\geq$ 1.5) risk factors included evidence of established vascular disease in the form of renal dysfunction (creatinine clearance < 40 mL/min), treated diabetes (receipt of insulin or oral hypoglycemic agents), and angina. Evidence (history or symptoms) of congestive heart failure and African-American ethnicity were also associated with increased risk for CHD events. Of interest, uncontrolled hypertension (systolic blood pressure $\geq$ 140 mm Hg or diastolic blood pressure $\geq$ 90 mm Hg) was the only "traditional" Framingham risk factor with high predictive value for CHD events; age and smoking were not associated with CHD events and low- and high-density lipoprotein cholesterol levels were only weakly associated (11). Controlled hypertension (history of hypertension with normal blood pressure) was not associated with increased risk, reaffirming the effectiveness of antihypertensive treatment in preventing CHD events in high-risk persons. Elevated lipoprotein(a) levels emerged as a novel risk factor only in the placebo group, since hormone replacement therapy is known to reduce lipoprotein(a) levels (12). The rate of coronary events ranged nearly sixfold, from 1.3% per year for women with no risk factors (except known CHD) to 8.7% per year for those with five or more risk factors.

Several limitations of HERS may have affected the risk assessment of the participants. Participation was voluntary, and exclusion criteria eliminated persons with unstable disease, thus leading to lower event rates and possible underestimates of risk. The age range of participants was narrow (mean [±SD], 67 ± 7 years), thus eliminating age as a risk factor. The small sample size of some subgroups (for example, only 13% were current smokers) limited the power to detect potentially meaningful differences. Concomitant treatment with lipid-lowering agents (53% at baseline and 66% at the end of the study) undoubtedly attenuated the predictive value of lipid measurements. The study did not include diagnostic tests, such as electrocardiography, echocardiography, and exercise testing, that would be used in practice to predict CHD outcomes in high-risk women. Finally, the statistical analysis of risk was not a prospectively designed element of HERS. As has been discussed, the post hoc data-driven design increases the probability that biologically meaningless associations will be revealed by chance (13). Despite these limitations, the analysis provides useful guidance for secondary prevention strategies in this understudied population.

The most striking aspect of Vittinghoff and colleagues' analysis was the alarming underuse of proven therapies for secondary prevention of cardiovascular disease. Despite clear indications for these therapies, few HERS participants received β-blockers (33% at baseline and 28% at the end

use of the system by its former and current mayors. Benefits have accrued to the CHC, the hospital, and, most important, the patients, with an improved continuum of care. Such integration of all components of the public health care system is critical to the survival of the safety net in this changing and complicated health care environment. In fact, integration has occurred in other safety net systems, such as Parkland in Dallas, Texas; Cook County in Chicago, Illinois; and Cambridge in Cambridge, Massachusetts.

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of the study) or angiotensin-converting enzyme inhibitors (18% at baseline and 28% at the end of the study), whereas more were given lipid-lowering agents (66% at the end of the study) and aspirin or other antiplatelet agents (83% at baseline and 79% at the end of the study). Paradoxically, women with more risk factors (≥5), and hence more potential benefit, were less likely than those with no risk factors to receive aspirin or other antiplatelet drugs (76% vs. 85%, respectively) or lipid-lowering therapy (59% vs. 72%, respectively) at the end of the study. This report confirms previous evidence that women with CHD are being undertreated in the United States (6).

Although HERS did not show cardioprotective effects of hormone replacement therapy in postmenopausal women, it did highlight a terrible discrepancy between what we know and how we treat our sisters and mothers. Current guidelines for secondary prevention of atherosclerotic cardiovascular disease include use of pharmacologic treatments to prespecified goals (blood pressure < 140/90 mm Hg, or lower if comorbid conditions are present; low-density lipoprotein cholesterol level < 100 mg/dL), as well as lifestyle modification for smoking cessation, regular physical activity, and weight and diabetes management (14). Evidence from randomized, controlled trials indicates that these interventions are effective in preventing CHD events in high-risk women (15–17). Furthermore, experience in the HERS cohort supports this conclusion: Rates of nonfatal myocardial infarction, CHD death, total mortality, and venous thromboembolic events were lower among statin users (18). In addition, recent evidence shows that lifestyle modification can prevent type 2 diabetes (19), reduce blood pressure or prevent clinical hypertension (20), and improve lipid profiles, thus reducing CHD risk and the need for aggressive pharmacologic therapies. Proven tools to prevent CHD events in women exist. A call to action is needed to implement them.

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